DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Cincinnati District Office
Central Region
6751 Steger Drive
Cincinnati, OH 45237-3097
Telephone: (513) 679-2700
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WARNING LETTER
CIN-WL-01-1405-0

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

June 11, 2001

John A. Kraeutler, President and COO
Meridian Bioscience, Inc.
3471 River Hills Drive
Cincinnati, Ohio 45244

Dear Mr. Kraeutler:

We are writing to you because during an inspection of your firm located at the above address by the Food and Drug Administration (FDA) on October 23, 2000/January 17, 2001, our Investigator collected information that revealed serious regulatory problems involving in-vitro diagnostic products that are manufactured and distributed by your firm.

Under the Federal Food, Drug, and Cosmetic Act (the Act), these products are considered to be medical devices. The law requires that manufacturers of medical devices conform with the requirements of the Quality System Regulation (QSR) as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

The inspection revealed that your firm's devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for the manufacture, processing, packing, storage or distribution are not in conformance with the requirements of the Quality System Regulation as follows:

Failure to validate and approve processes with a high degree of assurances and in accordance with established procedures when the results of a process cannot be fully verified by subsequent inspection and test. For example:

> Former Gull Laboratories (Gull) devices (Your firm acquired Gull in December 1998 and moved the Salt Lake City, UT operation to your Ohio location) are being manufactured and distributed before process validations have been completed. The lyophilization processes for Gull Immunofluorescent Assay (IFA) kits and for the Meridian Immunocard EIA kits and Fungal kits have not been validated. Since the lyophilization process cannot be fully verified by subsequent inspections and tests, it must be validated. Some examples of specific kits are Merifluor EBV Viral Capsid Antigen (VCA) IgM IFA, ImmunoCard Mycoplasma, and CALAS Pronase Reagent.

Process validation as implemented by your firm did not validate the operating process parameters. There was no data to establish operating conditions or ranges and no validation to ensure the product meets its specifications when the process is operated over the allowed range. For example, the vacuum drying process parameters for the Immunocard kits' cards have not been validated e.g., ImmunoCard *Clostridium difficile*, ImmunoCard *Helicobacter pylori*, and ImmunoCard Mycoplasma. The failure to properly or completely validate these processes could affect the stability or shelf life of the products.

Failure to establish and maintain process control procedures that include monitoring and control of process parameters and component and device characteristics during production. For example:

Monitoring and control of components during production were not being carried out, for all specimens for Gull IFA kits. The specimens were not being qualified and tracked as required by the "Specimen Identification Numbering System" procedure. Also, antibodies and antigens used to manufacture reagents were not being tracked as to the location of the freezer in which they are stored. In addition, the usage of these antibodies, antigens and specimens were not documented.

There was no documentation justifying the expiration dates and temperature storage assigned to antibody serum, purified antibodies, and antigens which are spotted on cards and microwells and /or are used to make enzyme conjugates. There was also no documentation of how (e.g., the amount of aliquots per container) these in-process components are stored.

There was a lack of control of the number of freeze/thaws that antibodies and antigens may undergo and there isn't any validation for how many freeze/thaws are allowed before these cycles will affect the performance of the product.

The following software used in the production process of your in-vitro diagnostic kits was not validated.

The [redacted] Database is used to process customer complaints. In addition, all trending of complaints is performed in the [redacted] Database. The [redacted] Database has not been validated nor does it include controls needed to assure authenticity and integrity of the electronic records in this open system.

The [redacted] Database used to track and trend all nonconformance reports and corrective and preventive action reports had not been validated. A Senior Manager for Quality Systems told the FDA Investigator that they could not find any manuals for this database.

Specifications for Purified Water U.S.P. did not include limits for objectionable microorganisms, such as Pseudomonas. Purified Water was being used for product make-up and reagents.

Failure to adequately investigate the cause of non-conformities relating to product, processes, and the quality system.

The activities to correct and prevent the Immunocard Mycoplasma test kit positive/negative controls problem, which led to the recall of several lots of this device, were inadequate. For example, the activities to correct and prevent the Immunocard Mycoplasma kit's test and control ports from exhibiting false negatives with the positive control and patient specimens, which led to the recall of lots 709030.091-709030.094 and 709030.097-709030.102 of the product in

March 2000 were inadequate in that the Corrective and Preventive Action Request (CAPAR) #0156, dated 5/12/00 stated to add a specification to the "Optimization of Mycoplasma Antigen for Spotting Cards" (PP0167) for the Mycoplasma Antigen concentration to be [redacted] Investigation INV0022 only validated a concentration of [redacted]

On or about August 4, 2000, the Finished Goods Supervisor authorized the use of the [redacted] lyophilizer and the other [redacted] lyophilizer to be used for the vacuum drying process for Immunocard Mycoplasma's cards with lot #7865.115. These lyophilizers had not been validated for use with this product. A Nonconforming Product Report (NCR #0304) was completed for these cards due to the vacuum achieved not being ≤[redacted] (All cards were scrapped.) The "Root cause" listed on the NCR was that "equipment did not achieve the ≤[redacted] required for IC Mycoplasma". The root cause should have stated that this lyophilizer had not been validated for this process. The Finished Goods Supervisor signed off on this non-conformance.

Failure to verify or validate corrective and preventative actions to ensure that such actions are effective and do not adversely affect the finished device.

For example: CAPAR #0185 with due date 5/9/00 states the "Labels are now 'read only' to the label clerks". This change in the computer system was not verified and/or validated. Although a "Retrospective Software Validation" was performed on the Product Labeling System in September 21, 2000, it does not address changing labels to be "Read only" for the label clerks. Procedure "Document and Document Change Control", SP1002.011 describes the "Read Only" directory for label clerks. No verification that this is "Read Only" had been performed.

Failure to establish and maintain procedures to control product that does not conform to specified requirements and failure to document the investigation of nonconforming product.

Nonconformance reports were not always completed and documented. When the ending temperature for the vacuum drying process for several lots of the cards in the Immunocard Mycoplasma kit was not within specifications, a nonconformance report was not prepared and the lots were distributed. Not following the vacuum drying procedure resulted in your firm recalling several lots of Immunocard Mycoplasma kits.

The following are 6 examples of the pull down vacuums for six lots of cards, which were manufactured between October of 1999 and January of 2000, not meeting the specification of less than or equal to [redacted]

-Mycoplasma ImmunoCard lot #7865.092 (part of kit lot # 709030.102, states the vacuum at completion of the vacuum drying process was [redacted].
-Mycoplasma ImmunoCard lot #7865.088 (part of kit lot # 709030.101, states the vacuum at completion of the vacuum drying process was [redacted]
-Mycoplasma ImmunoCard lot #7865.091 (part of kit lot # 709030.100, states the vacuum at completion of the vacuum drying process was [redacted]
-Mycoplasma ImmunoCard lot #7865.090 (part of kit lot # 709030.099, states the vacuum at completion of the vacuum drying process was [redacted]
-Mycoplasma ImmunoCard lot #7865.089 (part of kit lot # 709030.098, states the vacuum at completion of the vacuum drying process was [redacted]
-Mycoplasma ImmunoCard lot #7865.087 (part of kit lot #'s 709030.097 and .092, states the vacuum at completion of the vacuum drying process was [redacted].

Nonconforming reports were not completed for the above card lots for not meeting the vacuum of less than [redacted]

Failure to establish and maintain adequate procedures to control the design of a device in order to ensure that specified design requirements are met.

Design History Files had not been established for each type of device for which design changes were made and design changes were not being validated/verified before their implementation. For example, on July 26, 2000 a specification was added to the "Optimization of Mycoplasma Antigen for Spotting Cards" (PP0167). The specification was that the Mycoplasma antigen concentration is to be [redacted] There was no design history file for the Mycoplasma antigen used for spotting Immunocards. In addition, as discussed previously, this design change was not adequately verified/validated for optimization of Mycoplasma antigen concentrations below [redacted]

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the FDA inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for Class III devices to which the QS/GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

In order to facilitate FDA in making the determination that corrections to the deviations from the Quality System Regulation have been made and thereby enabling FDA to withdraw its advisory to other federal agencies concerning the award of government contracts, and to resume marketing clearance for Class III devices, and Certificates to Foreign Governments for products manufactured at your medical device facility, we are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device Quality System Regulation (21 CFR, Part 820). You should also submit a copy of the consultant's report, and certification by your establishment's Chief Executive Officer (if other than yourself) that he or she has reviewed the consultant's' report and that your establishment has initiated or completed all corrections called for in the report. The attached guidance may be helpful in selecting an appropriate consultant. We are aware that your firm is already utilizing the help of several consultants. If you so desire you may utilize their services to fulfill this request.

The initial certifications of audit and corrections and subsequent certifications of updated audits and corrections should be submitted to this office by the following dates:

- Initial certifications by consultant and establishment: November 1, 2001 (or sooner)
- Subsequent certifications of updated audits and corrections: November 1, 2002
  November 1, 2003.

We received the following documents from your firm in response to the inspection and/or Form FDA 483 dated January 17, 2001: a letter dated January 9, 2001 containing your Comprehensive Priority Action Plan, a letter dated February 9, 2001 containing your FDA-483 response, a letter dated February 27, 2001 containing your Master Revalidation Plan, and letters dated March 9, 2001, April 12, 2001, and May 16, 2001 containing monthly status reports on your firm's corrective action activities. We also met with you on three different occasions to discuss the QS/GMP deficiencies at your firm and your firm's plans/progress in correcting the deficiencies.

You have made some progress in correcting the deficiencies observed during the inspection, but you still have a long way to go. We acknowledge your firm discontinued manufacturing a number of products subsequent to the FDA inspection e.g., all Gull ELISA products, ImmunoCard C. difficile Toxin A, and ImmunoCard Rotavirus. However, many of the deficiencies discussed above are systemic, and, for the most part, directly relate to the medical devices your firm is still manufacturing/distributing. The "Master Interim Release QSR Compliance Plan" your firm has implemented as part of your "MDI's Comprehensive Priority Action Plan" includes continued manufacture and distribution of products even though their manufacturing processes have not been validated.

You stated in your response letters that most of the significant equipment and processes used in the manufacture of the Gull IFA kits at your facility are the same as those utilized by Gull prior to the transfer from Gull. We disagree. We believe that there are some significant differences in your present process and the process Gull was using e.g., the lyophilization process. The lack of validation of the lyophilization process in use at your facility for the Gull IFA kits that you are manufacturing and distributing could result in the failure to maintain an acceptable moisture content that could result in sub-potent or less active finished assays, as well as less stable assays for your firm's in-vitro diagnostic kits.

In a review of your firm's master revalidation plan it appears you are, in some cases, validating the process for specific products with one production run and are relying on the similarity among the products in a product family and/or the processes used to produce them to validate the process for all members of that family of products. There is an inherent danger in relying on perceived similarities between products, processes, and equipment without appropriate challenge. You should determine the differences between products and assure, statistically, that respective process differences are validated by your plan. For example, all eight of the Merifluor EBV products are shown as one family (Attachment 9 of your February 27, 2001 letter) and, according to your plan, each individual product will be subjected to one validation run. There appear to be considerable differences between the products, for example, [redacted]
Your validation of these processes must sufficiently challenge each product's process to assure with a high degree of certainty that each will meet its specifications between production runs.

You indicated in your response letters that the unvalidated process control software programs (the [redacted] and [redacted] Database programs) that your firm is using for tracking and compiling customers inquiries and nonconformance reports and corrective and preventive action reports will soon be replaced by a single software program that is compliant with 21 CFR Part 11. You indicated that your firm would validate the new software program ([redacted]

Your firm's "Master Interim Release QSR Compliance Plan" appears to rely on [redacted] stability testing as a basis for confirming the expiration dates for some of your devices for which the manufacturing process has not yet been validated. Stability testing must be performed on an adequate number of lots of products and each lot must be tested at appropriate intervals over several months or years to determine an appropriate expiration date. Testing samples from a single lot of your IVD devices and/or at a single

time interval would not provide sufficient information on the stability of your IVD devices to derive an appropriate expiration date.

We request that you take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed.

Your response to this Warning Letter should be sent to Evelyn D. Forney, Compliance Officer, Food and Drug Administration, 6751 Steger Drive, Cincinnati, Ohio 45237.

Sincerely,

Henry L. Fielden
District Director
Cincinnati District

Enclosure